IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: R. Zeman
CONTAG et al.	Group Art Unit: 1645
Serial No.: 08/844,336	Confirmation No.: 7227
Filing Date: April 18, 1997	Customer No.: 20855
Title: BIODETECTORS TARGETED TO SPECIFIC LIGANDS	

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is filed in response to the Final Office Action mailed May 28, 2010 and the Advisory Action mailed June 17, 2010. A Notice of Appeal was received in the USPTO on July 22, 2010, making an Appeal Brief due on or before September 22, 2010. Accordingly, this Appeal Brief is timely filed.

REAL PARTY IN INTEREST

The real party in interest is Xenogen Corporation, assignee of the instant application, as recorded in the USPTO at Reel 9497/Frame 0636 on October 6, 1998.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

STATUS OF CLAIMS

Pending: claims 1, 5, 6, 9, 21, 22 and 25 to 27

Canceled: claims 2-4, 7, 8, 10-20, 23 and 24

Appealed: claims 1, 5, 6, 9, 21, 22 and 25 to 27

STATUS OF AMENDMENTS

No amendments have been made subsequent to the mailing of the Final Office Action on May 28, 2010.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is drawn to a biodetector for the detection of a selected substance (specification, *e.g.*, at page 6, lines 18-19 and page 8, lines 13-20). The biodetector comprises: (a) a transmembrane fusion protein comprising an extracellular ligand-specific antibody moiety which binds to the selected substance and a protein-modifying membrane intracellular phosphatase or phosphorylase signal transforming domain, in which binding of the selected substance to the extracellular antibody moiety activates the phosphatase or phosphorylase (specification, *e.g.*, at page 6 lines 20-22; page 14, lines 23-26; and page 15, lines 8-27); (b) a transducer protein separate from the phosphatase or phosphorylase, the transducer having distinct inactive form and active forms, and in which the activated intracellular phosphatase or phosphorylase converts said inactive form of said transducer into the active form (specification, *e.g.*, at page 6, lines 22-23; page 11, lines 9-12; page 14, lines 23-29; page 15, lines 24-27; and page 16, lines 11-22); and (c) a responsive element comprising a nucleic acid encoding a light-

generating protein operably linked to a transcription activation element, wherein said responsive element is bound by and activated by said active form of said transducer, resulting in a detectable light signal (specification, *e.g.*, at page 6, lines 23-24; page 9, lines 22-23; page 9, lines 26-29; page 10, lines 1-16; page 11, lines 12-15; page 16, lines 16-22; page 14, lines 6-9 and 26-29; page 16, lines 18-20; and page 19, line 10 through page 22, line 21).

Claim 5 depends from claim 1 and further specifies that the light-generating protein is a bioluminescent or fluorescent protein (specification, *e.g.*, at page 16, lines 24-25).

Claim 6 depends from claim 5 and further specifies that the nucleic acid comprises a luciferase operon (specification, *e.g.*, at page 11, lines 15-18; page 17, line 18 through page 19, line 5; Figure 4; and Example 1).

Claim 9 depends from claim 6 and further specifies that the selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion (specification, *e.g.*, at page 9, lines 1-4; page 15, lines 1-3; and page 23, lines 2-29).

Claim 21 depends from claim 1 and further specifies that the intracellular enzymatic signal transforming domain is a PhoQ intracellular enzymatic domain (specification, *e.g.*, at page 15, lines 29-30).

Claim 22 depends from claim 1 and recites a genetically engineered bacterial cell comprising a biodetector according to claim 1 (specification, *e.g.*, at page 8, lines 27-29; page 11, lines 4-18).

Claim 25 depends from claim 1 and further indicates that the intracellular enzymatic signal transforming domain comprises an active domain of PhoQ (specification, *e.g.*, at page 15, lines 29-30).

Claim 26 depends from claim 1 and further indicates that that the transmembrane fusion protein is a fusion of an active domain of PhoQ, and a region of a heavy chain antibody (specification, *e.g.,* at page 15, lines 29-30; page 26, line 25 to page 27, line 18).

Claim 27 depends from claim 5 and further specifies that the light-generating protein is a bioluminescent protein (specification, *e.g.*, at page 16, lines 24-25; page 17, line 18 through page 19, line 5).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether, pursuant to 35 U.S.C. § 112, 1st paragraph, the specification provides adequate written description for the subject matter of claims 1, 5, 6, 21, 22 and 25 to 27.

ARGUMENTS

A. The claims are fully described by the as filed specification

Claims 1, 5, 6, 21-22 and 25-27 were again rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not adequately described by the as-filed specification. (Final Office Action, pages 2-6). In particular, it was again alleged that the claims encompass "limitless combinations" that have not been shown to work as biodetectors and that only the exemplified biodetectors are actually described. *Id.* It was also alleged that the specification teaches that one must "empirically determine" which combination of elements function as intended. (Final Office Action, page 3, citing pages 26-28 of the specification).

In response to Appellants arguments that the specification clearly evinces possession of the particularly claimed biodetectors, the Advisory Action stated (Box 11):

> The instant claims encompass biodetectors comprising limitless combinations of transmembrane fusion proteins (comprising an extracellular ligand binding domain [i.e. antibody] and a membrane intracellular enzymatic signal [i.e. a phosphatase or phosphorylase], transducers and responsive element which generates a detectable light signal. As disclosed in the specification, one must empirically determine which combination of components function as intended (see, pages 26-28 of the specification). Given the lack of guidance within the specification, the skilled artisan would not know which combination of elements would produce a biodetector that functions as claimed. Applicant is reminded that adequate written description requires more than a mere statement that is part of the invention and reference to a potential method of isolating it. The functional fusion protein itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Moreover, given that it is not known in the art which combination of elements would lead to a biodetector with the claimed functions, the *Capon* decision is not germane. Consequently, since the specification does not provide a correlation between structure (i.e., the combination of elements comprising the

claimed biodetector) and its claimed functions, the invention is not properly described as required by the statutes.

For the reasons of record, Appellants reiterate that that the as-filed specification amply describes the claimed subject matter.

It is well settled that the written description requirement is satisfied if the specification reasonably conveys possession of the invention to one skilled in the art. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). The disclosure must be read in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange,* 209 USPQ 288 (CCPA 1981). Moreover, the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976).

In the case on appeal, the rejection is premised on the assertion that the claims are so broad as to encompass "limitless combinations" with no guidance on how to make these combinations.

However, the Examiner errs in construing the claimed subject matter. The claims specify that the transmembrane fusion protein comprises an extracellular antibody moiety and an intracellular phosphorylase or phosphatase. Binding of the ligand to the extracellular antibody moiety activates the intracellular phosphorylase or phosphatase. The activated phosphorylase/phosphastase activates the transducer (via phosphorylation or de-phosphorylation) which binds to the promoter linked to the light-generating protein and regulates expression of the light-generating protein. Simply put, the claimed biodetectors make use of known signal transduction cascades.

Moreover, contrary to the Examiner's assertion, there are not a limitless number of combinations of these elements. In all cases, the transmembrane fusion protein must be made up of an antibody (extracellular) and phosphorylase or phosphatase (intracellular). Such transmembrane fusion proteins are exemplified with PhoQ.

Furthermore, the as-filed specification clearly shows possession of the specifically claimed biodetectors (page 11, lines 30-31; page 12, lines 4-9; page 14, lines 21-29; page 15, lines 24-28, emphasis added):

> Once bound to a ligand, an enzymatic cascade is activated that serves to transmit the signal.
>
> Furthermore, as the ligand-specific domain of the signal converting element of the biodetector system may be exchanged like a cassette, an unlimited number of biodetectors can be generated to recognize any desired or selected substance. Thus, the biodetectors of the present invention provide a flexible, generic system that can be adapted to recognize any selected substance, out of a wide variety of choices.
>
> The signal converting element is composed of an "extracellular" portion selectively binding a specific substance and an "intracellular" portion capable of activating the transducer. Typically, the signal converting element will be a transmembrane fusion protein composed of an extracellular ligand-binding portion, *e.g.,* an antibody and an intracellular enzymatic portion, which is activated upon binding of the extracellular portion to a selected target. Accordingly, the signal converting element is designed to convert the recognizing and binding of a specific substance, *i.e.,* ligand into an intracellular signal, resulting in the activation of the transducer component, which in turn activates a promoter that drives the expression of the reporter protein.
>
> ...The signal transforming domain may consist of an enzyme or active domain of an enzyme that has any number of protein modifying functions which may include phosphorylation, dephosphorylation, methylation, acetylation and protease activity. Such enzymes include protein kinases, phosphorylases, protein methylases, acetylases, proteases, proteinase K, serine proteases, among others.

In addition, the state of the art, as summarized in the specification, clearly evidences that the claimed antibody-phosphorylase/phosphatase transmembrane fusion proteins and their role in signal transduction were known (see, page 26, line 25 to page 27, line 18 of the as-filed specification, emphasis added):

> The fusion protein composed of an antibody heavy chain and a surface protein known to transduce signals for gene regulation, and a

promoter that is affected by this signal is placed in front of the marker gene. Antibody light chains are coexpressed in the biodetector to provide additional ligand specificity (Borrebaeck et al., 1992, *Biotechnology* 10:697-698). Bacterial phosphatase has been selected as the initial transmembrane and signal-transducing component of the gene fusion **because of its current use** in identifying surface expressed fusion proteins in bacteria (Kohl et al. 1990, *Nucleic Acids Res.* 18:1069; Weiss and Orfanoudakis, 1994; *J. Biotechnol.* 33:43-53) and a colorimetric substrate is available for measuring phosphastase activity. **Antibody fragment-phosphastase fusions have been generated with retention of both ligand binding specificity and phosphatase activity** (Kohl et al. 1991, *Acad. Sci.* 646:106-114; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). **Phosphastase-antibody fusions have been used to generate labeled antibodies for immunoassay** (Carrier *et al.,* 1995, *J. Immunol. Methods* 181:177-186; Ducancel *et al.,* 1993, *Biotechnology* 11:601-605; Weiss *et al.*, 1994; *J. Biotechnol.* 33:43-53; Weiss and Orfanoudakis, 1994; *J. Biotechnol.* 33:43-53; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). In additional antibodies to modified bacterial phosphatase have been shown to alter phosphatase function [citation omitted], indicating that protein-protein interactions can modulate phosphatase activity most likely through conformational changes in the phosphatase molecule. Expression of phosphatase fusion proteins on bacterial cell surfaces transduces a signal, phosphorylation into the cell which induced expression of specific genes. This system may be modified to tightly link the expression of marker proteins, luciferase and its accessory proteins, to binding of the ligand tot he antibody-phosphatase fusion protein, *i.e.,* a ligand-dependent molecular switch.

Therefore, the Examiner errs in asserting that the skilled artisan would not know how to combine an antibody and a phosphatase/phosphorylase domain into transmembrane fusion proteins as set forth in the claims. Indeed, because the use of such proteins in signal-transduction cascades was known, it is clear that Appellants were in possession of the claimed subject matter at the time of filing.

Furthermore, the Examiner errs in asserting that *Capon v. Esshar* 76 USPQ2d. 1078 (Fed. Cir. 2005) is not applicable to the case on appeal. In fact, the holding in *Capon* is particularly relevant to the instant case. In *Capon*, the Federal Circuit held that the precise sequence of a chimeric antibody need **not** be described because the components were well known (*Capon* at page 1085, emphasis added):

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. ...
>
> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

Thus, *Capon* is directly relevant to the pending case in which the Federal Circuit held that the precise sequence of a chimeric antibody need **not** be described because the components were well known. Likewise, in the instant case, the antibody and phosphorylase/phosphatase components of the chimeric transmembrane fusion protein which initiates a signal-transduction cascade intracellularly are also well known.

Appellants therefore strongly traverse the newly-raised assertion in the Advisory Action that *Fiers v. Revel* and *Amgen v. Chugai* are more germane to the case on appeal than *Capon*.[1] Both *Fiers* and *Amgen* addressed conception of cDNA sequences coding for specific proteins. The claimed biodetectors do not relate to cDNA sequences as in *Fiers* and *Amgen* and, accordingly, the fact-patterns in *Fiers* and *Amgen* are completely different than that of the case on appeal. In *Fiers* and *Amgen,* the claims were directed to sequences which were not disclosed in (or known prior to the filing of) the as-filed specification. In contrast, the pending claims are directed to biodetectors that are literally described in the specification and whose components were described in the specification and known in the art. Therefore, the findings in *Fiers* and *Amgen* have no bearing on the facts of the present application.

Again, although only *Capon* was addressed in the Advisory Action, the Federal Circuit decisions that are more germane to the case on appeal are *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000),

[1] It is noted that the Final Office Action's citation to *University of California v. Eli Lilly* was not reiterated in the Advisory Action, indicating that Applicants arguments in the response after final were persuasive.

Capon v. Eshhar, 76 USPQ2d 1078 (Fed. Cir. 2005) (discussed above), and *Falkner et al. v. Inglis et al.* 79 USPQ2d 1001 (Fed. Cir. 2006), all of which are must more recent than *Fiers* and *Amgen.*

In *Union Oil v. Atlantic Richfield*, the Federal Circuit made clear that the specification need **not** describe the exact chemical composition of every claimed combination, adding that neither the Patent Act nor case law requires such detailed disclosure (*see, Union Oil* at 1233):

> Appellant refiners assert that the specification does not describe the exact chemical component of each combination that falls within the range claims of the '393 patent. However, neither the Patent Act nor the case law of this court requires such detailed disclosure. ...
>
> The inquiry for adequate written description simply does not depend on a particular claim format, but rather on whether the patent's description would show those of ordinary skill in the ... art that the inventors possessed the claimed invention at the time of filing.

In *Falkner,* the Federal Circuit reaffirmed that working examples are not required to satisfy the written description requirement, even for a broad genus (*see, Falkner,* 1004):

> Specifically, we hold, in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

With particular regard to recitation of known structures, the Federal Circuit cited *Capon* in reaffirming that adequate written description does not require re-description of the sequence of known molecules and that literature available at the time of filing must be considered in determining the adequacy of the written description (*Falkner, Id.*):

> Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention. As we stated in Capon, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." Id. at 1358. Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (wherein permitted) of such genes and sequences.

The holding in *Falkner,* like the holdings in *Union Oil, Capon* (and the case law regarding written description generally), provides further support (if any is needed) that the written description rejection in the case on appeal is unsustainable in view of the specification as a whole and the state of the art as exemplified by the literature of record.

In light of these clear teachings of the Court, the Office's assertion, in the case on appeal, that Appellants are required to disclose multiple examples of particular biodetectors, is inconsistent with the requirements of the first paragraph of Section 112.[2]

Finally, the Examiner has improperly based a written description rejection on the grounds that embodiments must be "empirically determined." As noted by the Examiner, the written description requirement of Section 112 is separate from the enablement requirement. The written description requirement does not necessitate that Appellants list all possible embodiments (including embodiments that can be empirically determined). Rather, the relevant inquiry is whether the as-filed specification, in light of the state of

[2] Applicants also direct attention to Examples 9 and 14 of the PTO Guidelines on Written Description in which the Office clearly states that disclosure of a single representative species can adequately describe a broad genus. These Examples were favorably commented on by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

the art, shows that Appellants were in possession of the claimed subject matter at the time of filing.

For the reasons of record, it is clear that, in view of the state of the art regarding fusion proteins involved in cascades and the as-filed specification's clear disclosure in this regard, Appellants have shown possession of the claimed subject matter.

Furthermore, as noted above, the Federal Circuit reiterated in *Capon* and *Falkner*, because each component of the claimed proteins was well known and described, the claimed subject matter is adequately described. Appellants have clearly evinced possession of the components of the claimed biodetectors and, accordingly, have satisfied the written description requirement.

Moreover, Appellants also amply describe that which is new, *i.e.,* biodetectors as claimed using known transmembrane protein cascades. Thus, clear description is present in the original claims and specification, and the written description requirement has therefore been satisfied. Appellants have shown possession of the claimed subject matter at the time of filing – clearly and unmistakably. As a result, the rejection cannot be sustained.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are patentable. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: August 24, 2010

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CLAIMS APPENDIX

The claims on appeal are as follows:

1. A biodetector for the detection of a selected substance comprising:

(a) a transmembrane fusion protein comprising an extracellular ligand-specific moiety and a protein-modifying membrane intracellular enzymatic signal transforming domain, wherein said extracellular ligand-specific moiety comprises an antibody and wherein said antibody binds said selected substance, which binding activates said intracellular enzymatic signal transforming domain, wherein the membrane intracellular enzymatic signal transforming domain is a phosphorylase or a phosphatase;

(b) a transducer protein, wherein said transducer has an inactive form and an active form which are distinct from each other, and said activated intracellular enzymatic signal transforming domain converts said inactive form of said transducer into said active form of said transducer protein, wherein said transducer and said intracellular enzymatic signal transforming domain are separate proteins;

(c) a responsive element comprising a nucleic acid encoding a light-generating protein operably linked to a transcription activation element, wherein said responsive element is bound by and activated by said active form of said transducer, resulting in a detectable light signal.

5. The biodetector of claim 1, wherein said light-generating protein is a bioluminescent or fluorescent protein.

6. The biodetector of claim 5, wherein said nucleic acid comprises a luciferase operon.

9. The biodetector of claim 6, wherein said selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion.

21. The biodetector of claim 1, wherein said intracellular enzymatic signal transforming domain is a PhoQ intracellular enzymatic domain.

22. A genetically engineered bacterial cell comprising a biodetector according to claim 1.

25. The biodetector of claim 1, wherein said intracellular enzymatic signal transforming domain comprises an active domain of PhoQ.

26. The biodetector of claim 1, wherein said transmembrane fusion protein is a fusion of an active domain of PhoQ, and a region of a heavy chain antibody.

27. The biodetector of claim 5, wherein said light-generating protein is a bioluminescent protein.

EVIDENCE APPENDIX

No documents are submitted in the Evidence Appendix.

RELATED PROCEEDINGS APPENDIX

As noted above, Appellants are not aware of any related appeals or interferences. Accordingly, no documents are submitted with this Appendix.